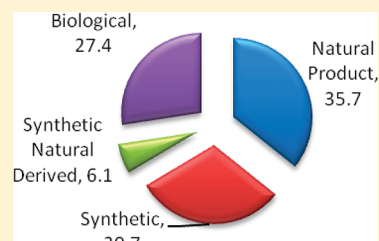


Natural Products As Sources for New Pesticides

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ABSTRACT: Natural products as pesticides have been reviewed from several perspectives in the past, but no prior treatment has examined the impact of natural product and natural product-based pesticides on the U.S. market, as a function of new active ingredient registrations with the Environmental Protection Agency (EPA). Thus, EPA registration details of new active ingredients for all conventional pesticide registrations and biopesticide registrations were compiled from the years 1997–2010. Conventional pesticide registrations and biopesticide registrations were examined both collectively and independently for all 277 new active ingredients (NAI) and subsequently categorized and sorted into four types: biological (B), natural product (NP), synthetic (S), and synthetic natural derived (SND). When examining conventional pesticides alone, the S category accounted for the majority of NAI registrations, with 78.0%, followed by SND with 14.7%, NP with 6.4%, and B with 0.9%. Biopesticides alone were dominated by NPs with 54.8%, followed by B with 44.6%, SND with 0.6%, and 0% for S. When examining conventional pesticides and biopesticides combined, NPs accounted for the majority of NAI registrations, with 35.7%, followed by S with 30.7%, B with 27.4%, and SND with 6.1%. Despite the common perception that natural products may not be the best sources for NAI as pesticides, when both conventional and biopesticides are examined collectively, and considering that NP, SND, and B all have origins from natural product research, it can be argued that their combined impact with the EPA from 1997 to 2010 accounted for 69.3% of all NAI registrations.



INTRODUCTION

The topic of natural products as pesticides has been reviewed from several perspectives in the past. Most of these papers have emphasized noncommercial products (see, for example, Duke et al.¹), and one covers only commercial products available in some parts of the world.² However, no prior review has examined the impact of natural product or natural product-based pesticides as a function of new active ingredient (NAI) registrations with the Environmental Protection Agency (EPA).

Four review articles have been published in the *Journal of Natural Products* since 1997 discussing natural products as sources of new drugs with an emphasis on new single chemical entity registrations.^{3–6} This article is intentionally modeled after these previous articles except with a focus on new pesticide active ingredients recently registered in the United States with the EPA. Many “categories of sources” used by Newman and Cragg have been applied in this article, with differences that will be discussed below.^{5,6}

Registration of pesticides in the United States with the EPA is governed by at least two federally mandated statutes, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)⁷ and the Federal Food, Drug, and Cosmetic Act (FFDCA).⁸ Essentially under the FIFRA, EPA registers pesticides for use in the United States and proscribes labeling and other regulatory requirements to prevent unreasonable adverse effects on human health or the environment, while under the FFDCA, EPA establishes tolerances (maximum legally permissible levels) for pesticide residues in food. Both Acts were amended significantly as a result of the Food Quality Protection Act of 1996 (FQPA),⁹ which changed fundamentally the manner in

which EPA regulates pesticides. The FQPA required EPA to complete periodic re-evaluations of pesticide registrations and tolerances. Part of this process involves “fact sheets” pertaining to new active ingredients, making information on the registration accessible to the public. For this reason, this review covers the period from 1997 to 2010 and examines the registration of new pesticide active ingredients only.

Federal law requires that before selling or distributing a pesticide in the United States, a person or company must obtain a registration, or a license, from the EPA. The EPA has currently separate review processes for three categories of pesticides: antimicrobials, biopesticides, and conventionals. “Antimicrobials” used in the context of this journal differs significantly from that intended by the EPA under this review process and is quite different from those processes for biopesticides and conventionals. In general, antimicrobial pesticides are substances or mixtures of substances used to destroy or suppress the growth of harmful microorganisms, whether they be bacteria, viruses, or fungi, on inanimate objects and surfaces. The key difference from biopesticides and conventionals is the indirect or nonspecific targeting by using such antimicrobials on inanimate objects and surfaces. New antimicrobials are not included in this review, and only new active ingredients proceeding through the biopesticide and conventional registration routes will be included.

According to the EPA, biopesticides include naturally occurring substances that control pests (biochemical pesti-

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Table 1. New Active Ingredient EPA Registrations for Conventional Pesticides from 1997 to 2010

chemical name	EPA chemical code	pesticide target	month issued	category ^a	chemical class	CAS number
acequinocyl	6329	mites	Sep-03	NP	quinoline	57960-19-7
acetamiprid	9050	insects	Mar-02	SND	neonicotinoid	135410-20-7
acibenzolar-S-methyl	61402	fungi (plant activator)	Aug-00	SND	benzothiadiazole	135158-54-2
alpha-chlorohydrin	117101	rodents	Dec-06	S	organochlorine	96-24-2
amicarbazone	114004	weeds	Oct-05	S	amide	129909-90-6
aminopyralid	5100	weeds	Aug-05	S	picolinic acid	150114-71-9
azoxystrobin	128810	fungi	Feb-97	SND	strobilurin derived	131860-33-8
benthiavalicarb-isopropyl	98379	fungi	Aug-06	S	carbamate	177406-68-7
bifenazate	586	mites	Jun-99	S	carbazate	149877-41-8
boscalid	128008	fungi	Jul-03	S	anilide	188425-85-6
bromuconazole	120503	fungi	Nov-02	S	triazole	116255-48-2
carfentrazone-ethyl	128712	weeds	Sep-98	S	aryl triazinone	128639-02-1
chlorantraniliprole	90100	insects	Apr-08	S	anthranilic diamide	500008-45-7
chlorfenapyr	129093	insects/mites	Jan-01	SND	pyrroles	122453-73-0
clodinafop-propargyl	125203	weeds	Jun-00	S	aryloxyphenoxypropiononic acid	105512-06-9
clofencet	128726	weeds	Feb-97	S	pyridazinecarboxlate	82691-71-0
cloransulam-methyl	129116	weeds	Oct-97	S	triazolopyrimidine	147150-35-4
clothianidin	44309	insects	May-03	SND	neonicotinoid	205510-53-8, 205510-92-5, 210880-92-5
copper octanoate	23306	fungi/bacteria	Jul-97	NP	fatty acid	20543-04-8
cuprous chloride	108303	fungi (plant growth regulator)	Sep-98	NP	copper salt	7758-89-6
cyazofamid	85651	fungi	Sep-04	S	cyanoimidazole	120116-88-3
cydalanilide	26201	plant growth regulator	May-97	S	malonanilate	113136-77-9
cyhalofop-butyl	82583	weeds	May-02	S	aryloxyphenoxypropiononic acid	122008-85-9
cymoxanil	129106	fungi	Apr-98	S	acetamide	57966-95-7
cyprodinil	288202	fungi	Apr-98	S	anilino-pyrimidine	121552-61-2
diclosulam	129122	weeds	Mar-00	S	triazolopyrimidine	145701-21-9
difenacoum	11901	rodents	Sep-07	SND	coumarin or chromenone	56073-07-5
diflufenzopyr	5108	weeds	Jan-99	S	semicarbazone	109293-97-2
dimethomorph	268800	fungi	Sep-98	S	morpholine	110488-70-5
dinotefuran	44312	insects	Sep-04	SND	neonicotinoid	165252-70-0
dithianon	99201	fungi	Sep-06	S	quinone	3347-22-6
epoxiconazole	123909	fungi	Aug-06	S	triazole	135319-73-2
ethaboxam	90205	fungi	Sep-06	S	triazole carboxamide	162650-77-3
etoxazole	107091	mites	Aug-02	S	diphenyloxazoline	153233-91-1
famoxadone	113202	fungi	Jul-03	SND	strobilurin derived	131807-57-3
fenazaquin	44501	insects/mites	Aug-07	S	quinazoline	120928-09-8
fenhexamid	90209	fungi	May-99	S	hydroxyanilide	126833-17-8
fenpropimorph	121402	fungi	Mar-06	S	amine	67564-91-4
flazasulfuron	119101	weeds	Mar-07	S	pyrimidinylsulfonylurea	104040-78-0
florasulam	129108	weeds	Sep-07	S	sulfonanilide	145701-23-1
fluazinam	129098	fungi	Aug-01	S	phenylpyridinamine	79622-59-61
flubendiamide	27602	insects	Aug-08	S	diamide	272451-65-7
flucarbazone	114009	weeds	Sep-00	S	triazolone	181274-17-9
flufenacet	121903	weeds	Apr-98	S	oxyacetamide	142459-58-3
flufenoxuron	108203	insects/mites	Sep-06	S	benzoylurea	101463-69-8
flumioxazin	129034	weeds	Apr-01	S	dicarboximide	103361-09-7
fluopicolide	27412	fungi	Mar-07	S	benzamide	239110-15-7
fluoxastrobin	28869	fungi	Nov-05	SND	strobilurin derived	361377-29-9
fluoroxypyr	128959	weeds	Sep-98	S	triazolone	69377-81-7
fluthiacet-methyl	108803	weeds	Apr-99	S	N-phenyl-phthalimide	117337-19-6
foramsulfuron	122020	weeds	Mar-02	S	pyrimidinylsulfonylurea	173159-57-4
forchlorfenuron	128819	plant growth regulator	Sep-04	S	phenyl urea	68157-60-8
fosthiazate	129022	nematodes	2004	S	organophosphate	98886-44-3
furfural	43301	fungi	Sep-06	S	furancaboxaldehyde	98-01-01
GnRH	116800	contraception	Sep-09	B	protein	9034-40-6

Table 1. continued

chemical name	EPA chemical code	pesticide target	month issued	category ^a	chemical class	CAS number
imazamox	129171	weeds	May-97	S	imidazolinone	114311-32-9
imazosulfuron	118602	weeds	Dec-10	S	sulfonylurea	
imiprothrin	4006	insects	Mar-98	SND	pyrethroid	72963-72-5
indaziflam	80818	weeds	Jul-10	S	fluoroalkyltriazine	950782-86-2
indoxacarb	67710	insects	Oct-00	S	oxadiazines	173584-44-6
iodomethane	11	fungi	Oct-07	S	alkyl iodide	74-88-4
ipconazole	125628	fungi	Sep-04	S	triazole	125225-28-7
isoxaflutole	123000	weeds	Sep-98	S	isoxazole	141112-29-0
kasugamycin	230001	fungi	Sep-05	NP	antibiotic fungicide	6980-18-3
kresoxim-methyl	129111	fungi	Sep-98	SND	strobilurin derived	143390-89-0
lithium perfluorooctane sulfonate (LPOS)	75004	insects	Aug-99	S	PFOS	29457-72-5
<i>Macleaya</i> extract	69095	fungi	Sep-02	NP	alkaloid	112025-60-2
mandipropamid	36602	fungi	Jan-08	S	amide	34726-62-2
meptyldinocap	36000	fungi	Sep-09	S	dinitrophenol	131-72-6
mesosulfuron-methyl	122009	weeds	Mar-04	S	pyrimidinylsulfonylurea	208465-21-8
mesotrione	122990	weeds	Jun-01	SND	triketone	104206-82-8
metconazole	125619	fungi	Aug-06	S	triazole	125116-23-6
methyl neodecanamide (MNDA)	79052	insects (repellent)	Jul-99	S	tertiary amide	105726-67-8
metofluthrin	109709	insects	Sep-06	SND	pyrethroid	240494-70-6
metrafenone	325	fungi	Sep-06	S	benzophenone	220899-03-6
nicarbazin	85712	avian contraception	Nov-05	S	pyrimidine	330-95-0
<i>N,N</i> -diethyl-2-(4-methylbenzyloxy) ethylamine hydrochloride	69089	plant growth regulator	Jan-00	S	methylbenzyloxy ethylamine	
novaluron	124002	insects	Sep-01	S	benzoylphenyl urea	116714-46-6
orthosulfamuron	108209	weeds	Feb-07	S	pyrimidinylsulfonylurea	213464-77-8
penoxsulam	119031	weeds	Sep-04	S	triazolopyrimidine	219714-96-2
phosphine	66500	insects	Dec-99	S	inorganic	7803-51-2
picaridin	70705	insects (repellent)	2001	S	piperidine	119515-38-7
pinoxaden	147500	weeds	Jul-05	S	phenylpyrazole	243973-20-8, 99607-70-2
pirimicarb	106101	insects	Feb-97	S	carbamate	23103-98-2
prohexadione calcium	112600	plant growth regulator	Apr-00	S	cyclohexadione	127277-53-6
propazine	80808	weeds	Sep-98	S	chlorotriazine	139-40-2
propoxycarbazone-sodium	122019	weeds	Jun-04	S	triazolone	181274-15-7
prothioconazole	1133961	fungi	Mar-07	S	triazole	178928-70-6
pymetrozine	101103	insects	Aug-00	S	pyridine azomethines	123312-89-0
pyrasulfotole	692	weeds	Aug-07	S	benzoylpyrazole	365400-11-9
pyridalyl	295149	insects	Apr-08	S	unclassified	179101-81-6
pyroxsulam	108702	weeds	Feb-08	S	triazolopyrimidine	422556-08-9
saflufenacil	118203	weeds	Aug-09	S	uracil	372137-35-4
spinetoram	110008/110009	insects	Oct-09	NP	spinosyn	187166-40-1/ 187166-15-0
spinosad	110003	insects	Feb-97	NP	spinosyn	131929-60-7, 131929-63-0
spirodiclofen	124871	insects/mites	Aug-05	S	tetronic acid	148477-71-8
spirotramat	392201	insects	Jun-08	S	tetronic acid	203313-25-1
sulfentrazone	129081	weeds	Feb-97	S	aryl triazinone	122836-35-5
tebufenpyrad	90102	insects/mites	Aug-02	S	pyrazole	119168--77-3
tembotrione	12801	weeds	Sep-07	SND	triketone	365400-11-9
tetraconazole	120603	fungi	Apr-05	S	triazole	112281-77-3
thiacloprid	14019	insects	Sep-03	S	chloronicotinoid	111988-49-9
thiazopyr	129100	weeds	Feb-97	S	pyridine	117718-60-2
thiencarbazone-methyl	15804	weeds	Oct-08	S	triazolone	317815-83-1
tolylfluanid	309200	fungi	Sep-02	S	sulfenamide	731-27-1
topramezone	123009	weeds	Aug-05	SND	triketone	210631-68-8
tralkoxydim	121000	weeds	Dec-98	S	cyclohexene oxime	87820-88-0
trifloxystrobin	129112	fungi	Sep-99	SND	strobilurin derived	141517-21-7
zoxamide	101702	fungi	Mar-01	S	benzamide	156052-68-5

^aNP = natural product; B = biological; SND = synthetic natural derived; S = synthetic.

cides), microorganisms that control pests (microbial pesticides or biocontrol agents), and pesticidal substances produced by plants containing added genetic material (plant-incorporated protectants, or PIPs).¹⁰ Conventional pesticides are perhaps the most familiar, and those that do not fall into the above categories would likely, but not always, proceed through the conventional registration route. Microbial pesticides are not covered, as most of these are living organisms and cannot be considered natural products in a chemical sense. Also, genetically modified plants that express pesticidal proteins (e.g., *Bacillus thuringiensis* toxin and virus coat proteins) or large polypeptides (proteins) are not discussed, as this type of compound is not commonly the subject of papers in this journal. Additionally, plant growth regulators are approved by the EPA under the same rules as pesticides although they are not used for pest management. While these compounds are listed for “plant control”, they are not discussed in this review. Some of the products that are mentioned are crude extracts, for which little is known of the active ingredient(s). Lastly, inorganic compounds are not discussed.

It is worth noting that an additional category of “minimum risk” pesticides are exempt from registration under section 25(b) of FIFRA. This short list includes the oils, both steam-distilled and/or pressed oils, from castor, cedar, cinnamon, citronella, cloves, corn, cottonseed, garlic, geranium, lemongrass, linseed, mint, peppermint, rosemary, sesame, soybean, and thyme; the inorganics sodium chloride, and zinc metal strips; the pure components citric acid, eugenol, geraniol, lauryl sulfate and its corresponding sodium lauryl sulfate, 2-phenethyl propionate, and potassium sorbate; and a few others such as corn gluten meal, dried blood, malic acid, putrescent whole egg solids, and white pepper. Despite the fact that numerous products containing these “active ingredients” are often commercialized, they are not included in this review because they are not new active ingredients.

This review is intended to document the impact of natural products and natural components on new pesticide active ingredient discovery and subsequent EPA registration. By examining the source for new pesticide active ingredients recently registered with the EPA, the impact of natural products on the pesticide industry will be illustrated. However, there is a paucity of peer-reviewed literature concerning many of the biological EPA-approved compounds and materials. It is also intended that this review may be used as a starting point for similar evaluations of the impact of natural products on the pesticide industry in the future and in countries other than the United States. Such analyses of the impact of natural product research on the discovery of commercialized pesticides may aid in appreciation of the “real world impact” of this research by both public and private research organizations.

■ RESULTS

In order to examine the impact of natural products and natural components on new pesticide active ingredient discovery and subsequent EPA registration, EPA registration details for all conventional pesticide registrations and biopesticide registrations were compiled. Publically available information provided by the EPA in the form of either spreadsheets or fact sheets was used to locate and tabulate the new active ingredients registered from the period of 1997 to 2010 (Table 1).^{11,12}

Major Categories of Sources. Categories of sources are defined as follows and were modeled on those categories previously used by Newman et al.^{5,6}

Biological “B”: usually a large peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host. Also includes whole organisms for biopesticides.

Natural Product “NP”: unmodified natural compound or crude preparation.

Synthetic “S”: totally synthetic in origin.

Synthetic Natural Derived “SND”: developed on the basis of a natural product pharmacophore.

Conventional Pesticides. Sorting of all EPA new active ingredient pesticides, registered from 1997 to 2010, using the conventional pesticide registration route, revealed a total of 109 registrations (Table 1). Eighty-five of these fell into the S category, with 16 SND, seven NP, and only one B. Consequently, 78.0% are S, 14.7% are SND, 6.4% are NP, and 0.9% are B (Figure 1). This will be contrasted later in the review when discussing biopesticide registrations as well as the total number of biopesticides and conventional pesticides.

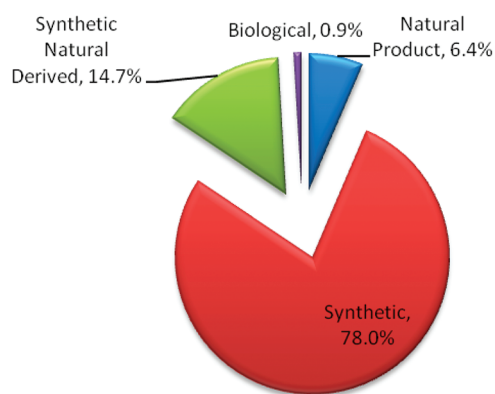


Figure 1. New active ingredient registrations for conventional pesticides from 1997 to 2010, organized by source.

Conventional Pesticides: Fungal Management. One group of fungicides registered through the conventional pesticides route has been derived from natural products. They are all derivatives of strobilurins, of which at least eight natural forms have been found (strobilurins A through H). These natural compounds are produced by several basidiomycete fungi, *Strobilurus tenacellus*, *Xerula* spp., and *Cyphellopsis anomala*.¹³ They inhibit electron transfer in mitochondrial respiration by binding to the ubiquinol (Q_o) site of cytochrome *b*. Those derivatives approved during the period 1997 to 2010 include kresoxim-methyl (1), trifloxystrobin (2), azoxystrobin (3), famoxadone (4), and fluoxastrobin (5) (Figure 2). These active ingredients are found in a large number of commercial agricultural fungicide formulations that are used on many crops to protect against a wide range of plant pathogens.

Kasugamycin (6, Figure 2) was first isolated from the soil actinomycete *Streptomyces kasugaensis*.¹⁴ It is sold as a hydrochloride salt form and inhibits binding of aminoacyl-tRNA to the mRNA-30S and -70S ribosomal subunit complexes, thereby inhibiting protein synthesis.¹⁵ It is a systemic fungicide that can be used to treat infected plants, as well as prevent the infection of crops, and was approved for use in Japan before being approved for use in the U.S.

An extract of the leaves of pink plume poppy (*Macleaya cordata*), sold as a fungicide, contains the alkaloids sanguinarine (7), chelerythrine (8), protopine, and allocryptopine.¹⁶ Of

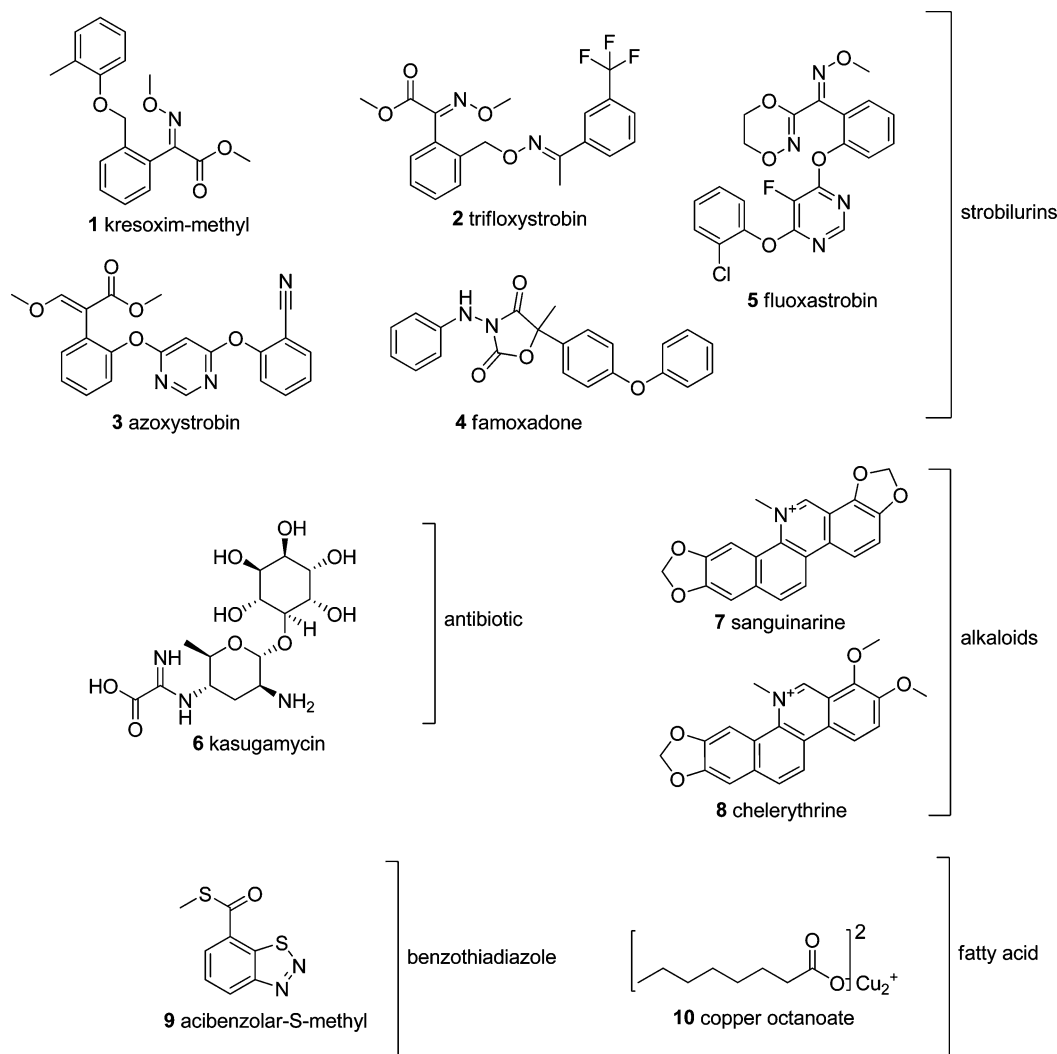


Figure 2. New NP and SND fungal management active ingredients registered using the conventional pesticide route from 1997 to 2010.

these, the first two are quite potent fungicides and bacteriocides in vitro (Figure 2).

Acibenzolar-S-methyl (9, Figure 2) appears to be derived synthetically from the natural product plant elicitor salicylic acid,¹⁷ despite the fact that no literature reports could be found directly claiming this. However, this compound is described clearly as a structural analogue of salicylic acid, is useful in the control of downy mildew on leafy vegetables, and works by inducing host plant resistance.

Copper octanoate (10, Figure 2) is formulated as a soap for plant pathogen control. Numerous patents were found for the use of this salt as a fungicide, but only one peer-reviewed paper discussing its use as an agricultural fungicide was retrieved.¹⁸

Conventional Pesticides: Insect Management. Conventionally registered new active ingredient insecticides and insect repellents that are either NP or SND fall into five main classes of chemicals: pyrethroids, neonicotinoids, pyrroles, quinolines, and spinosyns (Figure 3). The last-named category, spinosyns, are the only group of unmodified natural products, while the other four groups are synthetic substances based on original natural product lead compounds.

The SND pyrethroids, imiprothrin (11) and metofluthrin (12), are two of many synthetic pyrethroids in a long line of synthetics. The origins of the pyrethroid class of compounds

can be found in the traditional Chinese usage of powdered flowers from *Chrysanthemum* spp. for controlling insects.¹⁹ The bioactive natural compounds were mixtures of esters of cyclopropane carboxylic acids, primarily consisting of pyrethrins I and II, on which molecules of all synthetic pyrethroids are based. The pyrethrins are recommended for control of a wide range of insects and mites on fruit, vegetables, field crops, ornamentals, glasshouse crops, and house plants, as well as in public health, stored products, and animal houses and for domestic and farm animals. The global market share for pyrethroid pesticides in 2004 was estimated at 19%. The impact of pyrethroids on insect pest control worldwide cannot be overstated. Pyrethroids function via a neurotoxic action, which blocks voltage-gated sodium channels in nerve axons. As a result, the symptoms of pyrethroid poisoning are characterized by hyperexcitation, convulsions, seizures, and finally followed by death.²⁰ Unfortunately, the natural pyrethrins are unstable when exposed to air or ultraviolet light.

Neonicotinoids are another group of natural product-derived pesticides with a large impact on the worldwide insecticide market share.²⁰ During the time period for this review, three new active ingredients within this group were registered with the EPA: acetamiprid (13), clothianidin (14), and dinotefuran (15). Nicotine in the form of tobacco extracts was reported in

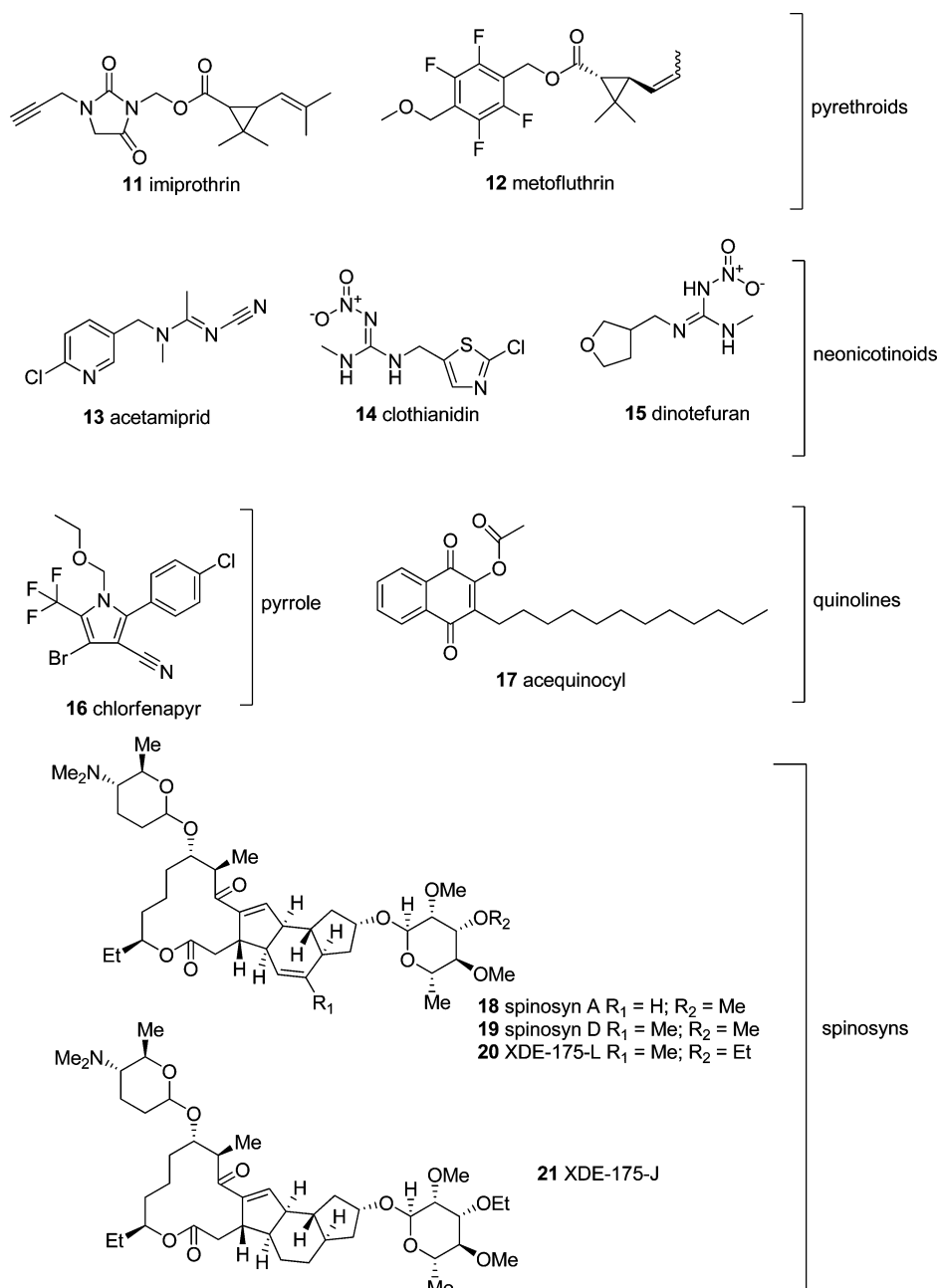


Figure 3. New NP and SND insect and mite management active ingredients registered using the conventional pesticide route from 1997 to 2010.

1690 as a plant-derived insecticide.²¹ Nicotine is still used as a minor insecticide and more recently as the active ingredient in organic-based insecticides. The lead compound for the neonicotinoids, 2-(dibromonitromethyl)-3-methylpyridine, was discovered in 1970 by Shell Development Company and eventually led to the production of this large group of highly effective synthetic insecticides. Neonicotinoids work as agonists on nicotinic acetylcholine receptors and show selective toxicity for insects over vertebrates.²²

One pyrrole, chlorfenapyr (**16**), was registered during the time period of this review. Chlorfenapyr (**16**) is a derivative of the natural product dioxapyrrolomycin obtained from an actinomycete, *Streptomyces* sp.²³ Chlorfenapyr (**16**) is a propesticide activated by the oxidative removal of the *N*-ethoxymethyl group, whereby the active *N*-dealkylated metabolite inhibits ATP production by disrupting the proton

gradient in oxidative phosphorylation within the mitochondria.²³

The quinoline, acequinocyl (**17**), was also registered during the time period of this review as a “reduced risk” miticide. “Reduced risk” registration of conventional pesticides typically proceeds at an expedited rate since such pesticides pose less risk to human health and the environment than existing conventional alternatives. Acequinocyl (**17**) is related structurally to the natural naphthoquinones and apparently derived from such compounds.²⁴ The activity of acequinocyl (**17**) is due to its deacetylated hydrolysis product, which inhibits complex III binding at the Q_0 center and blocks cellular respiration.²⁵

The emergence of the natural product spinosyns to the commercial marketplace in recent years has had a huge impact on insect control, and most products containing such

compounds are also approved for use in organic farming operations. Spinosyn products all appear to be unmodified natural products in the form of refined mixtures or extracts (Figure 3). Spinosyns registered during this time period include spinosad, which was originally isolated from the fermentation of the soil actinomycete *Saccharopolyspora spinosa*. Spinosad is a mixture of at least two major compounds, spinosyn A (18) and spinosyn D (19), with spinosyn A (18) being the major constituent. More recently, another spinosyn product, spinetoram, has been registered, and this is yet another fermentation product of *S. spinosa* and consists of a mixture of XDE-175-L (20) and XDE-175-J (21) (Figure 3). Spinosad and, by extension, spinetoram appear to be effective by both ingestion and contact and cause excitation of the insect nervous system, leading to involuntary muscle contractions, prostration with tremors, and finally paralysis. These effects are consistent with the activation of nicotinic acetylcholine receptors by a mechanism that is novel.^{26,27}

It should be mentioned that the discovery of one of the synthetic insecticides listed, flubendiamide, was based on the elucidation of the molecular target site of the complex alkaloid ryanodine [ryanodiol 3-(pyridine-3-carboxylate)] from the plant *Ryania speciosa*.²⁸ Although the structure of the synthetic compound is not based on that of the natural insecticide, it was discovered with in vitro bioassays of the Ca^{2+} -ryanodine receptor complex required for insect muscle function. Insecticides that target this complex are considered very safe for mammals.

Conventional Pesticides: Weed Management. As illustrated in previous sections of this review, natural products have had a significant impact on the development of a number of conventional pesticides. However, this has not been the case for herbicides. Only one class of natural product-derived herbicide has been registered since 1997, namely, the triketone herbicides.

The discovery and development of these herbicides followed a fairly convoluted path that began in 1977 when Reed Gray at Stauffer Chemical observed that the bottlebrush plant (*Callistemon citrinus*) repressed the growth of other plants in its surroundings, suggesting that it might produce a strong allelopathic agent. Bioassay-guided isolation work led to the discovery that leptospermone, a previously characterized acyl syncarpic acid plant metabolite with no known biological activity, caused stunting and bleaching of grass seedlings. The herbicidal activity of leptospermone and a number of synthetic alkanoyl syncarpic acid analogues was patented subsequently in 1980.²⁹

During this period of time, other investigators were developing new acetyl-coenzyme A carboxylase inhibitors. Some of the structures had no herbicidal activity but instead protected plants against injury caused by thiocarbamate herbicides. Further modification of this chemistry led to moderately herbicidal cyclohexane-1,3-diones that caused similar bleaching of green tissues to leptospermone. Ultimately, the syncarpic acid unit of leptospermone was combined with the benzoyl moiety of these other compounds to obtain compounds with much higher overall herbicidal potencies and weed-controlling spectra. The resulting commercial triketone herbicides [i.e., mesotrione (22), topramezone (23), and tembotrione (24); Figure 4] are broad-spectrum, bleaching herbicides, active on both grass and broadleaf weeds, that were optimized from this class of compounds.³⁰

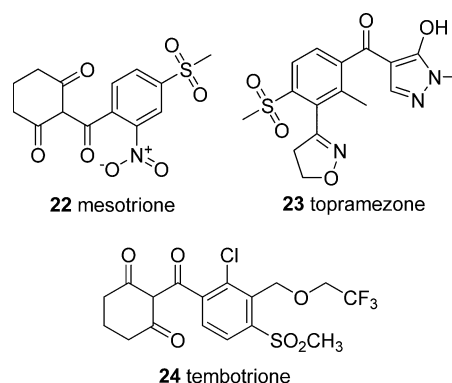


Figure 4. New SND weed management active ingredients registered using the conventional pesticide route from 1997 to 2010.

Until the discovery of triketone herbicides, all bleaching herbicides except one (clomazone) targeted phytoene desaturase (PDS), a key enzyme in carotenoid synthesis. While triketone herbicides caused bleaching on meristematic tissues and increases in phytoene levels similar to PDS inhibitors, they did not inhibit phytoene desaturase.

Elucidation of the unique site of action of the triketones was made following advances regarding the biological activity of structural analogues in mammalian systems, where they inhibited *p*-hydroxyphenylpyruvate dioxygenase (HPPD), the enzyme that catalyzes the formation of homogentisate (HGA), the first committed step in tyrosine catabolism. Plant HPPD proved to be the target of triketone herbicides.³¹ However, inhibition of HPPD in plants disrupts the biosynthesis of carotenoids and results in bleaching (loss of chlorophyll) of the foliage of treated plants. In plants, the product of HPPD catalysis, HGA, is a key precursor of α -tocopherol and plastoquinone. The latter prenylquinone is a required cofactor for phytoene desaturase.³² Therefore, inhibition of HPPD indirectly reduces phytoene desaturase activity by reducing the pool of available plastoquinone.³³ The subsequent decrease in carotenoid levels results in the destabilization of the photosynthetic apparatus. Accordingly, under high light intensity, excess energy is no longer quenched, chlorophyll molecules are destroyed, and the foliage is bleached.

The basic triketone backbone apparently mimics a reaction intermediate of HPPD, rendering these structures time-dependent (tight-binding) inhibitors. A number of structure–activity relationships leading to the development of the conventional HPPD inhibitors have been published.^{30,34–36} More recently, our group reported that the natural triketone components of manuka oil (*Leptospermum scoparium*) were indeed inhibitors of HPPD, but they differ in potency against this enzyme.³⁷ A follow-up study with a number of naturally occurring leptospermone and grandiflorone and natural analogues showed that a C_9 alkyl side chain gave an $I_{50\text{app}}$ value of 19 ± 1 nM. This is significantly more active than the commercial herbicide sulcotrione, which showed an $I_{50\text{app}}$ value of 250 ± 21 nM. The most active naturally occurring β -triketone, grandiflorone, exhibited an $I_{50\text{app}}$ value of 750 ± 70 nM.³⁸

Conventional Pesticides: Other. Difenacoum (25, Figure 5) is a derivative of coumarin, belonging to the 4-hydroxycoumarin class of anticoagulant rodenticides. Several other coumarin-based rodenticides were approved for use in

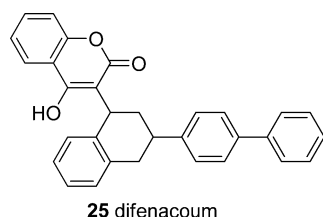


Figure 5. New SND rodenticide active ingredients registered using the conventional pesticide route from 1997 to 2010.

the United States, beginning with warfarin, before the period covered by this review.

Biopesticides. During the time period covered by this review, there were approximately 168 new active ingredient biopesticide registrations (Table 2). Among these, 92 were categorized as natural products, 75 as biologicals, and one as synthetic natural product derived, while none were synthetic. Nearly all of the biopesticides classified as biological are in fact plant-incorporated protectants (PIPs) aside from the few included in Table 2.

The real impact of natural product-based pesticides is exemplified in Figure 6, where new active ingredient registrations have been organized for conventional pesticides and biopesticides from 1997 to 2010 by source. The single largest source category is that of natural products, at 35.7%, followed by synthetics with 30.7%, biologicals with 27.4%, and, last, synthetic natural derived at 6.1%. If one were to consider also the biologicals as also “natural”, then the total impact of natural-derived products on pesticide discovery from 1997 to 2010 is 66.4% of the 277 new active ingredients.

Biochemical: Fungal Management. Polyoxin D is an antibiotic produced by the soil microbe *Streptomyces cavaoi* var. *asoensis*.³⁹ It kills fungi by inhibiting the chitin synthase enzyme.⁴⁰ The compound is produced from a fermentation culture and then purified in the form of polyoxin D zinc salt.

Diallyl sulfides are odiferous compounds found in onions and garlic.⁴¹ They are used to stimulate white rot spore germination in the absence of an onion or garlic crop in order to protect later onion, shallot, leek, or garlic crops from damage by this pathogen.⁴² The fungicidal activity of deoiled oriental mustard seed (Table 2) is apparently due to allyl isothiocyanate.⁴³

Rhamnolipid surfactants are fungicidal glycolipids produced commercially by *Pseudomonas aeruginosa*.^{44,45} The commercial fungicide contains two molecules, one a rhamnose ring with a fatty acid tail and the other with two rhamnose rings and a fatty acid tail.

A preparation of the saponins of *Chenopodium quinoa* has been registered for use against plant pathogens. These saponins are active against *Botrytis cinerea*.⁴⁶ Similarly, a crude preparation of saponins from the plant *Quillaja saponaria* is fungicidal to several plant pathogens.⁴⁷ A mixture of crude extracts of Southern red oak (*Quercus falcata*), fragrant sumac (*Rhus aromatica*), red mango (*Mangifera indica*), and prickly pear cactus (*Opuntia* spp.) was approved for use against nematodes and fungal pathogens. We found no scientific literature dealing with the efficacy of this preparation.

Laminarin is a storage glucan, produced by the brown alga *Laminaria digitata*.⁴⁸ It is a linear polysaccharide composed of $\beta(1\rightarrow3)$ -glucan with $\beta(1\rightarrow6)$ -linkages. It is not fungitoxic, but induces host defenses in treated plants to ward off fungal pathogens.⁴⁹

Yeast extract hydrolysate is approved for use to prevent fungal plant pathogen infections of crops. Although no scholarly articles were found on this product, chitin, a yeast cell wall constituent, is known to induce resistance of plants to plant pathogens.⁵⁰

Several related compounds (glycerol monocaprylate, glycerol monocaprate, glycerol monolaurate, propylene glycol monocaprylate, propylene glycol monocaprate, and propylene glycol monolaurate) have been approved for use against mites and fungi. Similar emulsifiers have been shown to retard the growth of plant pathogens,⁵¹ and this group of harpin and harpin $\alpha\beta$ proteins is listed for “plant control” (i.e., plant growth regulator) by the EPA, as seen in Table 2. However, these products are used primarily for plant pathogen management, not plant growth regulator purposes. Harpin, a protein from the bacterium *Erwinia amylovora*, induces systemic acquired resistance to plant pathogens.⁵² Harpin $\alpha\beta$, a protein composed of four fragments from various bacterial plant pathogens, is produced heterologously in *Escherichia coli*. Its mode of action is the same as harpin from *E. amylovora*.

Biochemical: Insect Management. Nearly half (43%) of the biochemical biopesticides appear to be registered for controlling insects. Of these, approximately 25, or 32%, of the insect-controlling biopesticides covered during this period are derived from insect pheromone discoveries such as verbenone produced by the pine bark beetle or the many lepidopteran (butterflies and moths) pheromones such as (Z)-11-tetradecenyl acetate, just to name a few (Table 2). Most are used to disrupt the mating behavior of certain moths of which the larvae destroy crops and trees. It is not within the scope of this review to discuss each of these pheromones.

Many of the insect-controlling biochemical biopesticides function as insect repellents, such as 3-(N-butyl-N-acetyl)-aminopropionic acid, ethyl ester (IR3535), *p*-menthane-3,8-diol (PMD), and L-carvone. IR3535 and PMD have been used in Europe for some time and were only recently introduced to the U.S. market. PMD appears to be produced synthetically for most commercial products in which it is present. However, its original source was from the oil of the lemon-scented eucalyptus, *Corymbia citriodora*.⁵³ PMD may have been more successful were it not for issues with eye irritation. IR3535 is related structurally to natural β -alanine, and according to an EPA factsheet, it is “functionally identical to naturally occurring beta-alanine in that both repel insects, the basic molecular structure is identical, the end groups are not likely to contribute to toxicity and it acts to control the target pest via a non-toxic mode of action”. L-Carvone is a major constituent of *Mentha spicata* and is also used to repel mosquitoes. Additional insect-repelling biochemical biopesticides can also be found in Table 2, such as 4-allylanisole, present in many herbs, catmint oil from *Nepeta cataria*, and methyl eugenol from cloves.

At least one product from this time period is a product of the neem tree, *Azadirachta indica*. Cold pressed neem oil is one of many commercially available formulated neem products.

Biochemical: Weed Management. A number of biochemical herbicides have been registered with the EPA since 1997. Horticultural vinegar, which consists of diluted aqueous solutions of acetic acid (up to 20% v/v), is commercialized as a burn-down product for nonselective weed management. It is used primarily on non-cropland areas, but can be employed in other settings as a selective spray. The relatively high concentration to provide greater than 80% control of weeds is often cost-prohibitive for large-scale agriculture. Furthermore,

Table 2. New Active Ingredient EPA Registrations for Biochemical Biopesticides^a from 1997 to 2010

EPA name	EPA chemical code	pesticide type	month issued	category ^b
(E)-11-tetradecen-1-ol acetate	129019	insects	Feb-97	NP
(E)-9-dodecen-1-ol acetate	119004	insects	May-99	NP
(E,Z)-3,13-octadecadien-1-ol (56336–48)	129117	insects	Apr-06	NP
(E,Z)-7,9-dodecadien-1-yl acetate		insects	Apr-10	NP
(E,Z,Z)-3,8,11-tetradecatrienyl acetate		insects	Sep-10	NP
(Z)-11-hexadecenyl acetate	129101	insects	Aug-01	NP
(Z)-11-tetradecenyl acetate	128980	insects	Feb-97	NP
(Z)-6-heneicosen-11-one	129060	insects	Jan-05	NP
(Z)-9-tetradecen-1-ol	119409	insects	Sep-99	NP
(Z,E)-9,12-tetradecadien-1-yl acetate (56336–47)		insects	Mar-06	NP
(Z,E)-9,12-tetradecadienyl acetate	117203	insects	Sep-99	NP
(Z,Z)-11,13-hexadecadienal	000711	insects	Jan-00	NP
(Z,Z)-3,13-octadecadien-1-ol (56336–48)	129118	insects	Apr-06	NP
(Z,Z,E)-7,11,13-hexadecatrienal	29000	insects	Apr-10	NP
1,7-dioxaspiro-(5,5)-undecane (olive fly pheromone)	124851	insects	Sep-03	NP
2,6-bis(1-methylethyl)-naphthalene (2,6-DIPN)	055803	sprout inhibitor	Oct-03	NP
2-methyl-1-butanol	431602	insects	Feb-10	NP
3-(N-butyl-N-acetyl)-aminopropionic acid, ethyl ester (IR3535)	113509	insects	Feb-99	NP
3-methyl-2-cyclohexene-1-one (MCH)	219700	insects	Jun-99	NP
4-(or 5-)chloro-2-methylcyclohexane-carboxylic acid, 1,1-dimethyl ester (trimedlure)	112603	insects	Jun-01	NP
4-allylanisole	062150	insects	Sep-01	NP
9,10-anthraquinone	122701	mammals, birds	Dec-98	NP
abscisic acid		plant control	Feb-10	NP
acetic acid	044001	weeds	Feb-97	NP
aminoethoxyvinylglycine hydrochloride (AVG)	129104	weeds (plant growth regulator)	Apr-97	NP
ammonium bicarbonate	073401	insects	Jun-04	NP
ammonium nonanoate	031802	weeds	Sep-06	NP
<i>Bacillus thuringiensis</i> Vip3Aa20	006529	insects	Nov-08	B
balsam fir oil	129035	mammals	Apr-07	NP
black pepper oil	000669	mammals	Mar-04	NP
calcium acetate	011470	insects	Feb-10	NP
calcium lactate		insects	Feb-08	NP
California red scale pheromone	017703/017704	insects	Sep-04	NP
canola oil	011332	insects	Apr-98	NP
citronellol	167004	mites	Apr-04	NP
cold pressed neem oil	025006	insects	Oct-09	NP
corn gluten meal	100137	weeds	Sep-02	B
coyote urine (80917-1)	029007	mammals	Mar-06	B
Cry1Ac in MON 87701 (soybean) PIP Cry1Ac	87701	insects	Sep-10	B
cuelure	128916	insects	Sep-05	NP
diallyl sulfides (DADs)	129087	fungi	Jun-03	NP
dipotassium phosphate	176407	fungi	Sep-02	NP
E,E-9,11-tetradecadienyl acetate		insects	Aug-08	NP
extract of <i>Chenopodium ambrosioides</i>	599995	insects	Apr-08	NP
fish oil	122401	mammals, birds	Mar-98	NP
formic acid	214900	mites	Jan-99	NP
fox urine	80917-5	mammals	Dec-07	B
gamma-aminobutyric acid (GABA)	030802	weeds	Jan-98	NP
glycerol monocaprate	011291	mites, fungi	Sep-03	NP
glycerol monocaprylate	011292	mites, fungi	Sep-03	NP
glycerol monolaurate	011290	mites, fungi	Sep-03	NP
harpin proteins	006477	plant control	Apr-00	B
harpin $\alpha\beta$ protein	006506	plant control	Feb-05	B
heptyl butyrate	100247	insects	Dec-08	NP
homobrassinolide		plant control	Jun-10	NP
hydrogenated catmint oil	71654-20	insects	Dec-08	NP
indole	025000	insects	Jun-09	NP
indole-3-acetic acid		plant control	Aug-07	NP
iron (ferric) phosphate	034903	mollusks	Aug-97	NP

Table 2. continued

EPA name	EPA chemical code	pesticide type	month issued	category ^b
iron HEDTA	034702	weeds, algae, moss	Dec-08	NP
kaolin	100104	insects, mites, fungi, bacteria	Mar-98	NP
laminarin		fungi	Feb-10	NP
lavandulyl senecioate	036005	insects	Jan-10	NP
L-carvone	079500	insects	Sep-09	NP
L-glutamic acid	374350	weeds	Jan-98	NP
L-lactic acid		insects, fungi	Jun-09	NP
lysophosphatidylethanolamines (LPE)	105120	plant control	Mar-02	B
maple lactone (2-cyclopenten-1-one)	004049	insects	Sep-98	NP
methyl eugenol (81325-2)	203900	insects	Apr-06	NP
methylcyclopropene (MCP)	224459	plant control	Apr-99	NP
mono and dipotassium salts of phosphorus acid	076416	fungi	Nov-97	NP
n-tetradecyl acetate		insects	Dec-08	NP
octenol	069037/069038	insects	Jul-07	NP
oriental mustard seed (allyl isothiocyanate)	014921	nematodes, fungi	Dec-08	NP
oxypurinol	447509	insects	May-99	NP
piperine	043501	mammals	Mar-04	NP
plant extract 620	169007	nematodes, fungi	Apr-97	NP
p-menthane-3,8-diol (PMD)	011550	insects	Mar-00	NP
polyoxin D zinc salt	230000	fungi	Aug-97	B
potassium dihydrogen phosphate	076413	fungi	Aug-98	NP
potassium silicate (82100-2)	072606	mites, fungi, insects	May-06	NP
propylene glycol monocaprate	011289	mites, fungi	Sep-03	NP
propylene glycol monocaprylate	082704	mites, fungi	Sep-03	NP
propylene glycol monolaurate	011288	mites, fungi	Sep-03	NP
rhamnolipid biosurfactant	110029	fungi	Mar-04	NP
saponins derived from the seeds of <i>Chenopodium quinoa</i>	097094	fungi	Sep-05	NP
saponins of <i>Quillaja saponaria</i>	097094	fungi	Jul-07	NP
silver nitrate	072503	plant control	Sep-01	NP
sodium carbonate peroxyhydrate	128860	fungi, algae	Sep-02	NP
sodium ferric EDTA	139114	mollusks	Dec-08	NP
sorbitol octanoate (70950-3)	035400	insects	Jan-06	NP
sucrose octanoate esters	035300	mites, insects	Sep-02	NP
terpene constituents of the extract of <i>Chenopodium ambrosioides</i>	599995	insects, mites	Jun-10	NP
trimethylamine	221801	insects	Jun-09	NP
trypsin modulating oostatic factor	105403	insects	May-04	B
verbenone	128986	insects	Dec-99	NP
Vip3Aa19	006499	insects	Jun-08	B
VipCot	006499/006529	insects	Jun-08	B
xanthine	116900	insects	May-99	NP
yeast extract hydrolysate	100053	fungi, bacteria	Feb-04	B
Z-9-tetradecen-1-yl acetate; Z-11-tetradecen-1-ol; Z-11-tetradecenal (53575-31)		insects	Jan-07	NP
Z-7-tetradecen-2-one	127600	insects	Mar-09	NP

^aTable intentionally excludes both microbial and plant-incorporated protectant (PIP) biopesticides. ^bNP = natural product; B = biological.

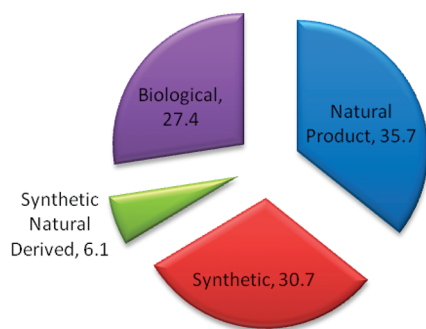


Figure 6. New active ingredient registrations for conventional pesticides and biopesticides from 1997 to 2010, organized by source.

the reduction in weed pressure is transient, as plants usually recover from the foliar damage, so repeated treatment with acetic acid is required to obtain a more sustained weed control.^{54,55}

The compounds gamma-aminobutyric acid (GABA) and L-glutamic acid are listed by EPA as biochemicals for weed management, but no literature was found on their herbicide use or any phytotoxicity of the compounds. Therefore, no data are presented for these compounds.

Corn gluten meal (CMG), an abundant byproduct of corn (*Zea mays*) mill processing, has broad-spectrum preplant incorporated and pre-emergence herbicide activity.^{56,57} CMG may be considered a slow-release proherbicide that releases phytotoxic dipeptides and a phytotoxic pentapeptide upon hydrolysis.^{58,59} It is commercialized under a variety of trade

names in products that contain between 50% and 100% of CGM.

CGM does not control existing weeds, but it has a broad-spectrum of activity on the germination and development of young emerging plants.^{60,61} However, control of weeds requires extremely high rates (e.g., 2 tons per hectare) and is often cost prohibitive. For example, partial control of 12 monocotyledonous and 10 dicotyledonous weed species required at least 324 g CGM/m², which corresponds to 3.2 tons/ha.⁶²

The herbicidal activity of fatty acids has been documented for years, and some fatty acid salts are now commercialized as nonselective herbicidal soaps.⁶³ Fatty acids with midrange aliphatic tails such as caprylic (C₈, octanoic acid) and pelargonic acid (C₉) are the most effective.⁶⁴ The ammonium salt of the medium-chain fatty acid pelargonic acid (commercialized under the name Racer) is a new contact bioherbicide that provides better control for broadleaf weeds than the monocot weeds. Nonanoate (pelargonic acid) causes rapid light-independent disruption of plant cell membranes that results in desiccation of the foliage.^{65,66} This bioherbicide is more efficacious than acetic acid or corn gluten meal, with herbicidal activity at 10–15 kg/ha.^{67,68} These herbicidal soaps are nonselective burn-down products with no residual activity and are often used as desiccants. Additionally, pelargonic acid has a low impact on the environment because of its low residual activity.

Biochemical: Other. Natural products approved for the management of mammals and birds are all repellents. Only two of these products are pure compounds. The compound 9,10-anthraquinone is an effective repellent for birds when sprayed on food sources.⁶⁹ For example, geese and other birds leave areas around airports when the grass that they normally eat is treated with 9,10-anthraquinone. Although this product is also listed for mammal control, the only pest listed on the EPA fact sheet is geese. The unpleasant odor and taste of piperine (produced in black peppercorns) is a repellent to mammals. Black pepper oil containing the same compound is also approved for this same use.⁷⁰ Other mammalian repellents recently approved are coyote urine, fox urine, balsam fir oil, and fish oil.

SUMMARY AND CONCLUSIONS

The present analysis of EPA registrations of new pesticides during the period 1997–2010 shows clearly that natural products play an important role in discovery and development of new products. Even among conventional pesticides, slightly over 20% are either natural products or natural product-derived substances (Figure 1). Broken down further, it is apparent that herbicides account for a small portion of this fraction (ca. 8% natural product derived), whereas about 30% of insecticides and fungicides are either natural product-derived or actual natural products (Figure 7). These fractions do not represent market share, but the triketone herbicides, the spinosyn, neonicotinoid, and pyrethroid insecticides, and the strobilurin fungicides have all been very successful products. Clearly, these successes will ensure that natural products will remain an important part of conventional pesticide discovery strategies. Excluding transgenes, biopesticides have a much smaller market share than conventional pesticides. Nevertheless, biopesticide use is growing. The reduced complexity and cost of gaining approval of a biopesticide as a commercial product partially explains the relatively large number of such products approved during the past decade (Table 2). Increasing demand for

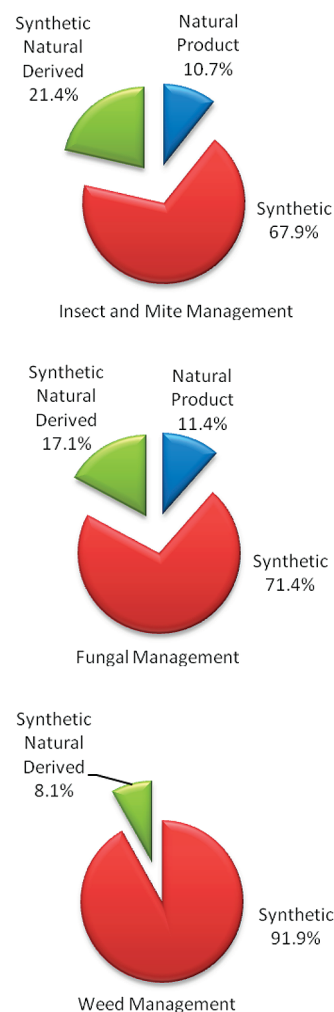


Figure 7. New active ingredient registrations for conventional insect and mite, fungal, and weed management from 1997 to 2010, organized by source.

“greener” pest management products is also fueling discovery and development efforts for new biopesticides.

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Notes

The authors declare no competing financial interest.

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